CAR T-cell therapy

Chimeric Antigen Receptor T-cell Therapy

for Multiple Myeloma

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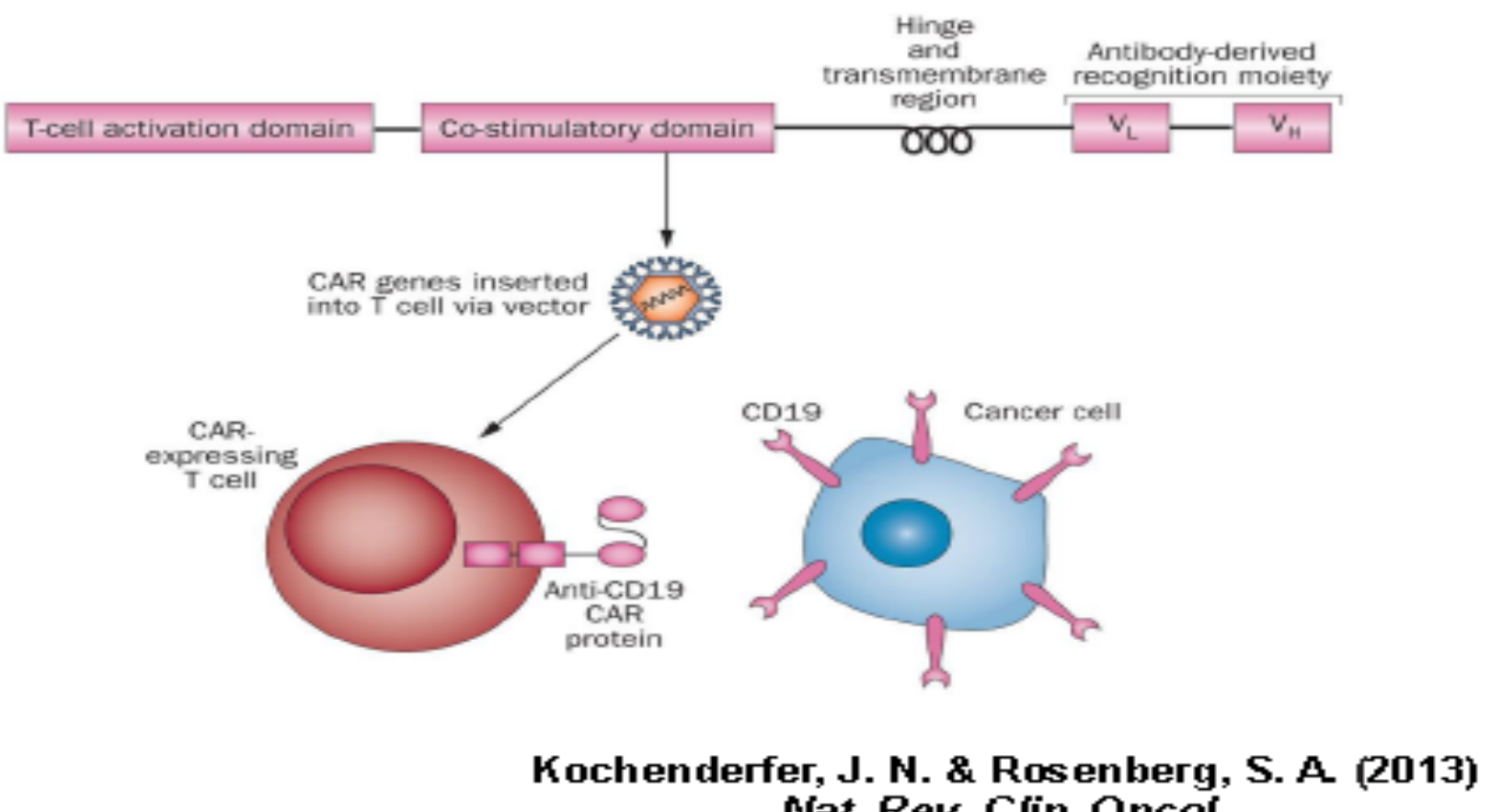
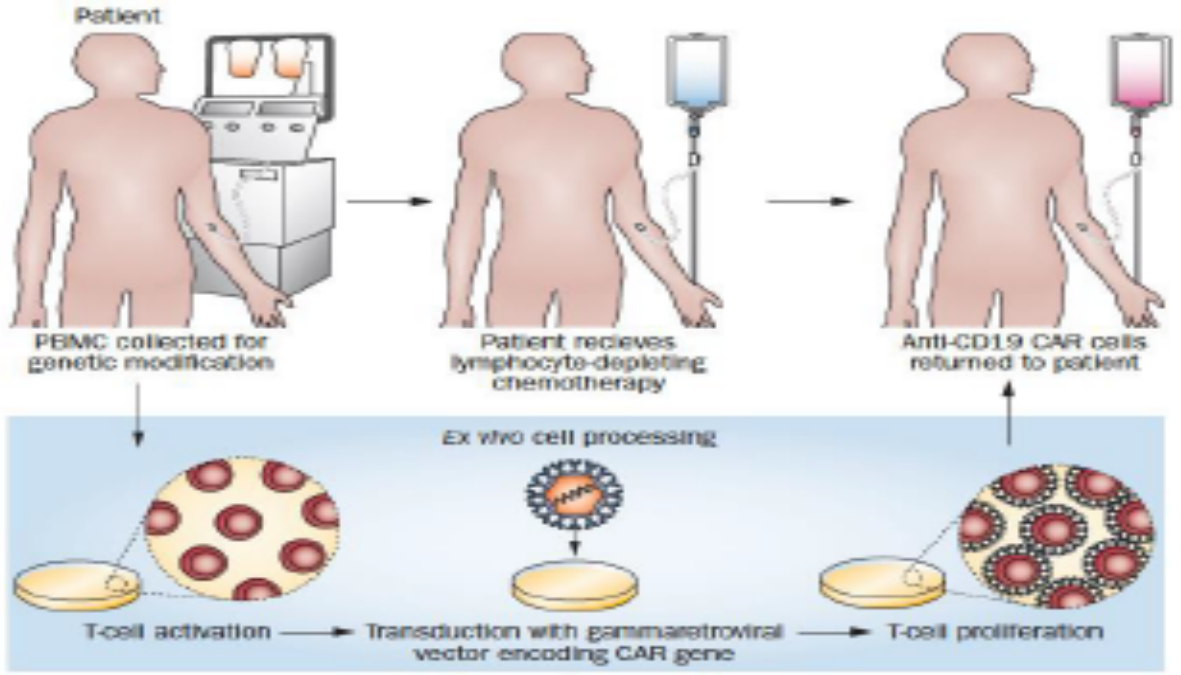
Chimeric antigen receptors (CARs)



Kochenderfer, J. N. & Rosenberg, S. A. (2013)
Nat. Rev. Clin. Oncol.

CARs

Chimeric Antigen Receptors (CARs)



Kochenderfer and Rosenberg, *Nature Reviews Clinical Oncology* 2013

CAR T-cell toxicities

CAR T cells can cause severe but reversible toxicities

- Cytokine release syndrome ("CRS")
  - Symptoms similar to sepsis due to infection or severe flu-like syndrome
  - High fevers
  - Tachycardia
  - Hypoxia
  - Hypotension
  - Decrease in liver or kidney function
  - Prolonged PTT, PT, DIC and ?risk of bleeding
  - Patients frequently require ICU admission
  - Usually occur in first 2 weeks but may occur a month following cell infusion
  - Can give IL-6 receptor antagonist tocilizumab +/- steroids

Neurological toxicities

CAR T cells can cause severe toxicities

- Neurologic Toxicities
  - Confusion
  - Somnolence
  - Tremors
  - Gait instability
  - Aphasia, other difficulties speaking
  - Seizures
  - Myoclonus and other focal motor defects
  - Cerebral edema on MRI → patient deaths
  - Neurologic toxicities may occur separately from CRS
  - Steroids are first line therapy

Toxicity grading system

CAR T-cell Toxicity Grading Systems

- **Historically, there has been no universal grading system for CRS**
  - NIH system
  - University of Pennsylvania system
  - MSKCC system
  - MD Anderson system
  - Difficult to compare toxicities between cell products
- **Neurotoxicity has been graded with the CTCAE system**
- **Recent attempt at a universal system for CRS and neurotoxicity (ASBMT committee)**
  - Lee et al., Biol Blood Marrow Transplant 2018

Guideline

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells

Daniel W. Lee[1,#], Bianca D. Santomasso[2,#], Frederick L. Locke[3], Armin Ghobadi[4], Cameron J. Turtle[5], Jennifer N. Brudno[6], Marcela V. Maus[7], Jae H. Park[8], Elena Mead[9], Steven Pavletic[6], William Y. Go[10], Lamis Eldjerou[11], Rebecca A. Gardner[12], Noelle Frey[13], Kevin J. Curran[14], Karl Peggs[15], Marcelo Pasquini[16], John F. DiPersio[4], Marcel R.M. van den Brink[8], Krishna V. Komanduri[17], Stephan A. Grupp[18,*], Sattva S. Neelapu[19,**]

Supportive care

Supportive Care for CAR T-cell Toxicity

Toxicity	Preventive/supportive measure
Fevers	• Acetaminophen • Cooling blankets • Avoid NSAIDs, steroids and meperidine
Cardiovascular	• At least q 4 hour vitals, q 2 if HR > 115 • IV fluid boluses for hypotension if SBP < 80% baseline and < 100 mm Hg, or if SPB < 90. • IVF to replace insensible losses; keep net positive • ECG, troponin, and Echo if patients require > 1 fluid bolus for hypotension or are in the ICU
ID	• PCP and HSV/VZV prophylaxis • Pan-culture for any fever • Pan-culture and broad spectrum antibiotics for neutropenic fever
Heme	• Allopurinol for tumor lysis syndrome prophylaxis • Goals: Hb > 8, platelets > 20, ANC > 500 (with filgrastim) • Goals: PTT normal; give FFP if > 1.5 x ULN; give cryoprecipitate for goal fibrinogen > 100.
Neurologic	• Neurology consult for all patients • Brain MRI and lumbar puncture whenever possible

Tocilizumab

Toxicity Management: Indications for Tocilizumab

- Tocilizumab is an IL-6 receptor antagonist used in rheumatologic disorders.
- Tocilizumab is the first-line agent for CRS at the NCI
- Dose is 8 mg/kg IV infused over 1 hour, not to exceed 800 mg.
- List of criteria for tocilizumab use on the adult service at NCI in the "CAR T-cell toxicity guidelines"
- No universal agreement on indications for tocilizumab
- Generally, consider tocilizumab for
  - Toxicities necessitating intensive care
  - Hypotension requiring vasopressors
  - Hypoxia requiring more than a nasal cannula, or significantly increased work of breathing
  - Consider for certain lab/study abnormalities: significant cardiac ejection fraction decrease, renal or hepatic failure, hyponatremia, coagulopathy, creatine kinase increase, etc.

Indications for corticosteroids

Toxicity Management: Indications for Corticosteroids

- In some studies, high dose corticosteroids were thought to decrease the activity of CAR T cells. For this reason, corticosteroids are reserved for refractory CRS and for neurologic toxicities.
- Dexamethasone 10 mg IV q 6 hours for severe neurologic toxicity
- Methylprednisolone: doses range from 50 mg IV q 6 hours to 1000 mg IV for refractory CRS
- No universal agreement on thresholds to give corticosteroids

Toxicity factors

Factors Associated with Toxicity

Lab Values that reflect severity of toxicity

- CRP
- LDH
- Ferritin
- DIC markers

- Higher peak blood levels of CAR T cells associated with more severe toxicity.

Possibly Contributing Inflammatory Cytokines

- Interferon-gamma
- IL-1
- IL-2, sIL-2-alpha
- IL-4
- IL-6
- IL-8
- IL-10
- IL-15
- TNF-alpha
- Granzyme B
- GM-CSF
- MIP-1-alpha
- MCP-1

Risk factors

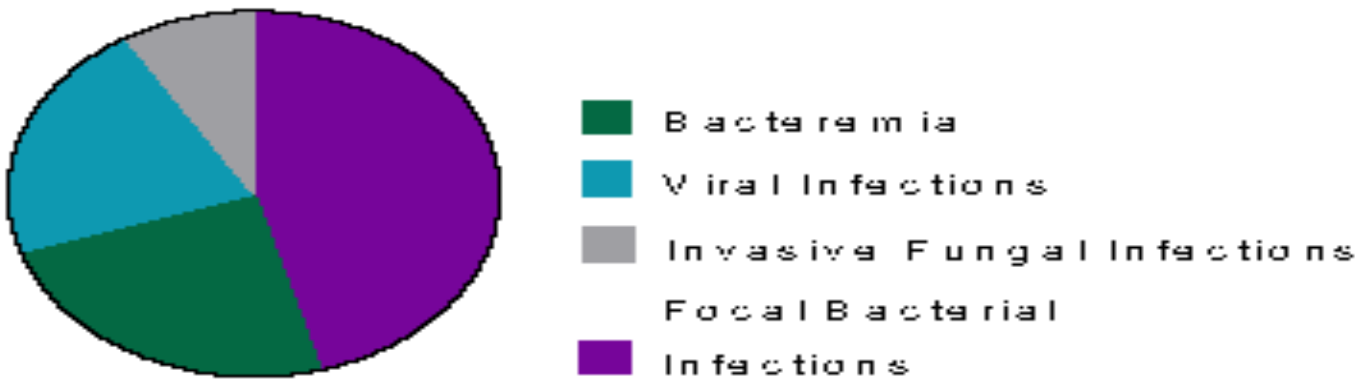
Toxicity Risk Factors

- Disease type: ALL vs NHL (possibly ALL more risk)
- Bone marrow involvement (higher → more risk)
- Burden of disease (higher → more risk)
- Type of lymphodepletion chemo (fludarabine → more risk? Or just better lymphodepletion → more risk?)
- Cell dose (higher → more risk)
- Costimulatory domain?/structure of CAR/antigen target (complex)
- Baseline markers of endothelial activation? (von Willebrand factor, ANG-2)

Infection risk

CAR T-cell Infection Risk

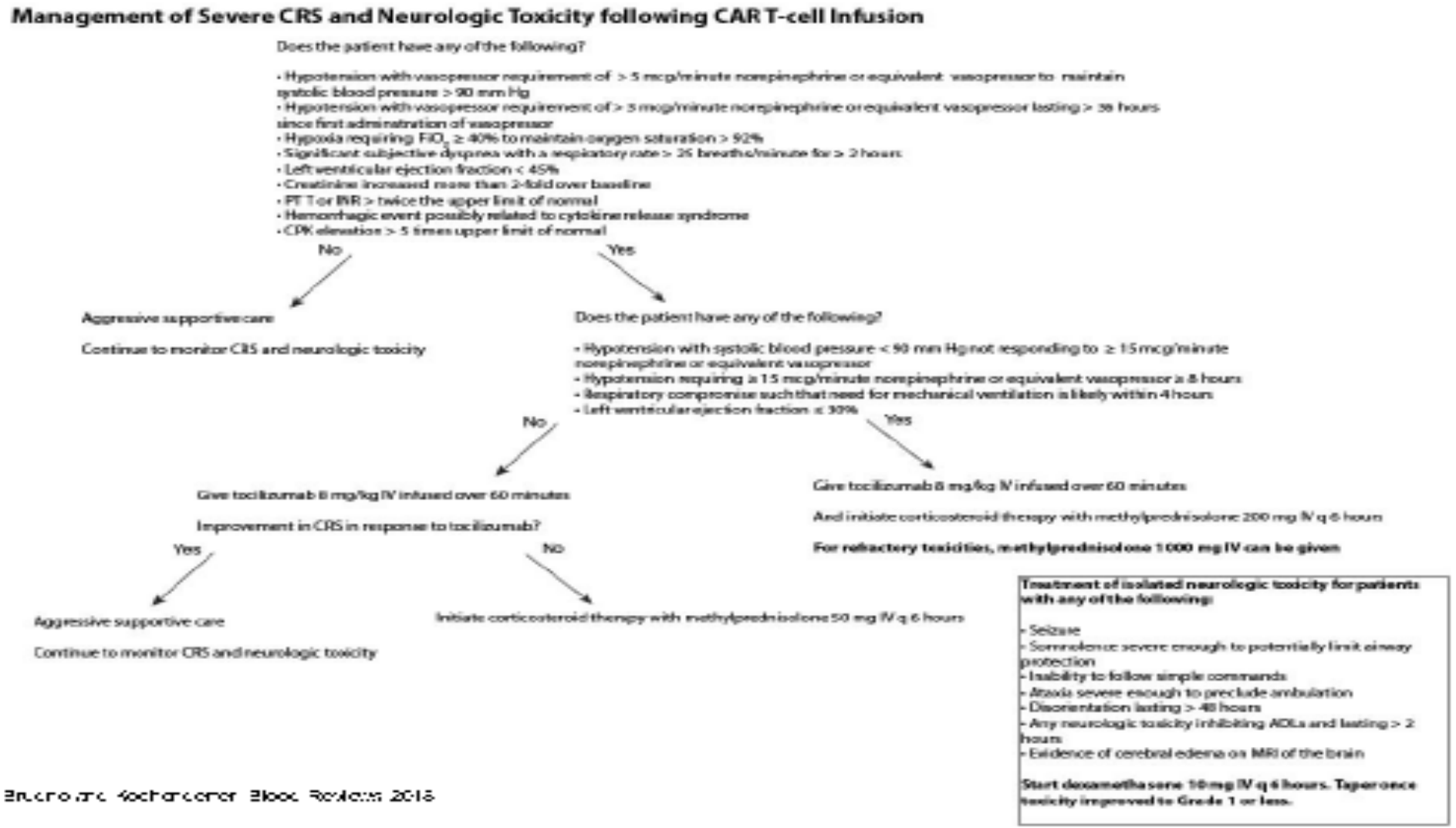
- CAR T-cell therapy patients may have a higher risk of infection within the first 30 and 100 days of therapy
- Underlying malignancy, # of prior lines of therapy, infections before infusion and presence of F&N post infusion were associated with a higher risk of infection.



103 INFECTIONS IN 58 PATIENTS ACROSS 4 TRIALS

Mikkilineni et al ASH 2019

Severe toxicity



Biol Blood Marrow Transplant. 2018

NIH specific thresholds

These are NIH-specific.

Thresholds to Give Immunosuppression Differ Among Institutions and the Landscape is Ever-Changing.

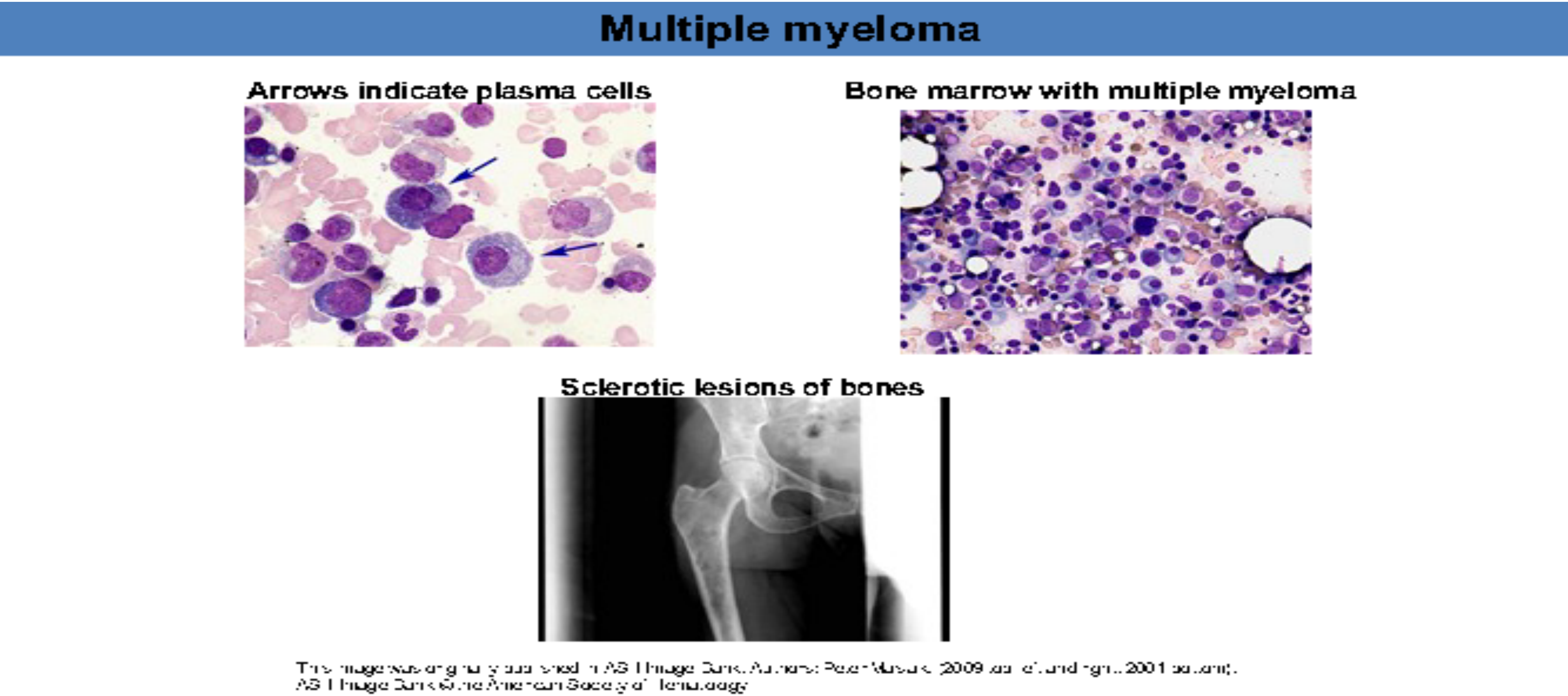
Biol Blood Marrow Transplant. 2018

B cell maturation antigen

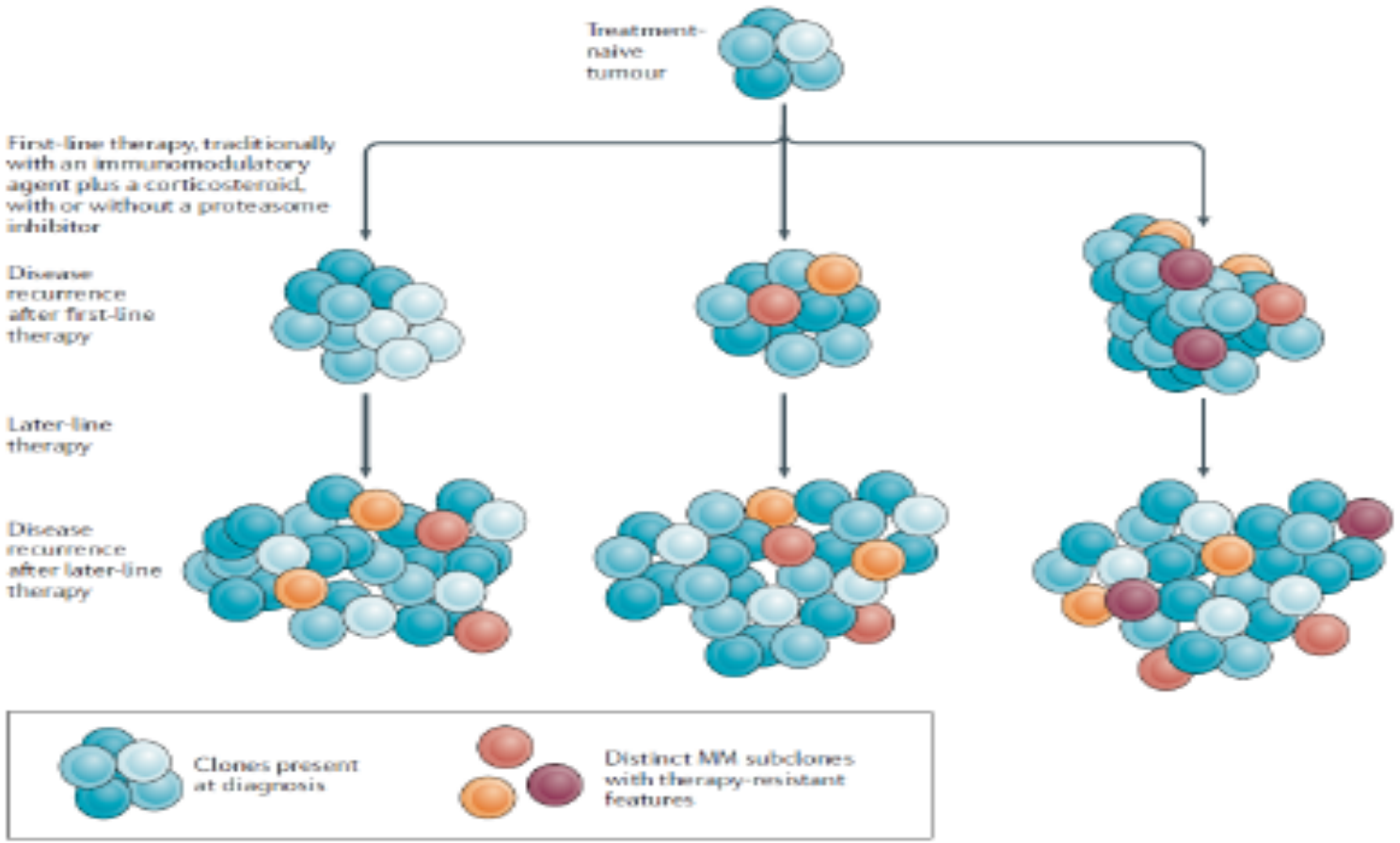
B-Cell Maturation Antigen a Target for

CAR T-cell Therapy of Multiple Myeloma

Multiple myeloma

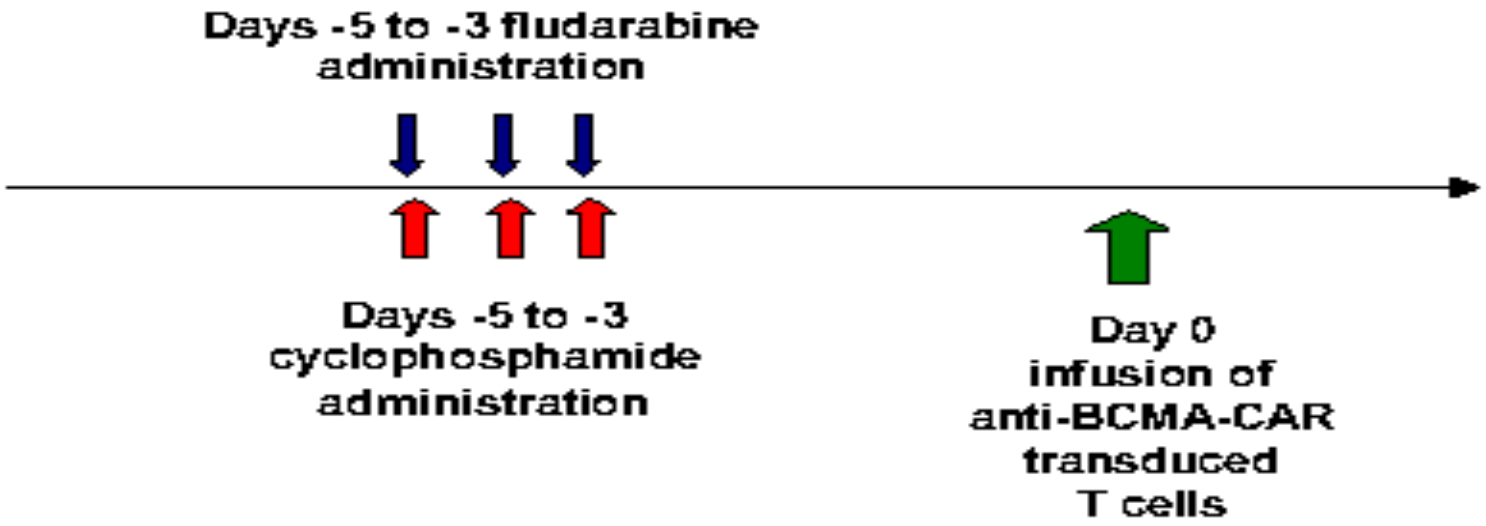


Multiple myeloma



Protocol design

Anti-BCMA CAR clinical protocol design



Cyclophosphamide: 300 mg/m² daily for 3 days

Fludarabine: 30 mg/m² daily for 3 days

B-cell maturation antigen

Development of the first CAR targeting B-cell maturation antigen (BCMA)

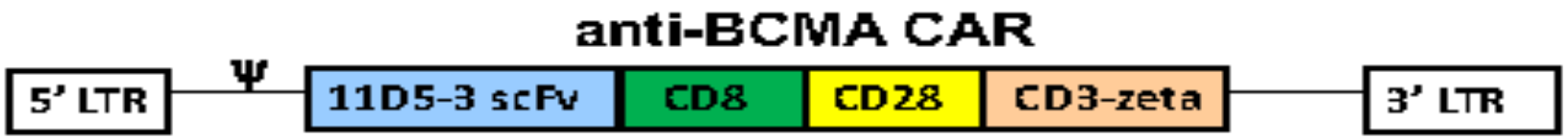
- BCMA (CD269) is a member of the TNF superfamily.
- By flow cytometry, BCMA is expressed on the myeloma cell surface by almost all cases of multiple myeloma.
- 34 different tissues were assessed by immunohistochemistry, BCMA was only expressed by plasma cells and a small fraction of B cells.
- We designed and tested the first series of anti-BCMA CARs

Carpenter et al. *Clinical Cancer Research*, 2013

T cell engineering

T cells can be genetically engineered to express an anti-BCMA chimeric antigen receptor

- We designed an anti-BCMA CAR and ligated it into a gamma-retroviral backbone.
- T cells were stimulated with the anti-CD3 monoclonal antibody OKT3 before transduction and cultured for 9 days before infusion.
- We initiated the first-in-humans clinical trial of an anti-BCMA CAR in 2014



Ali et al. *Blood*, 2016

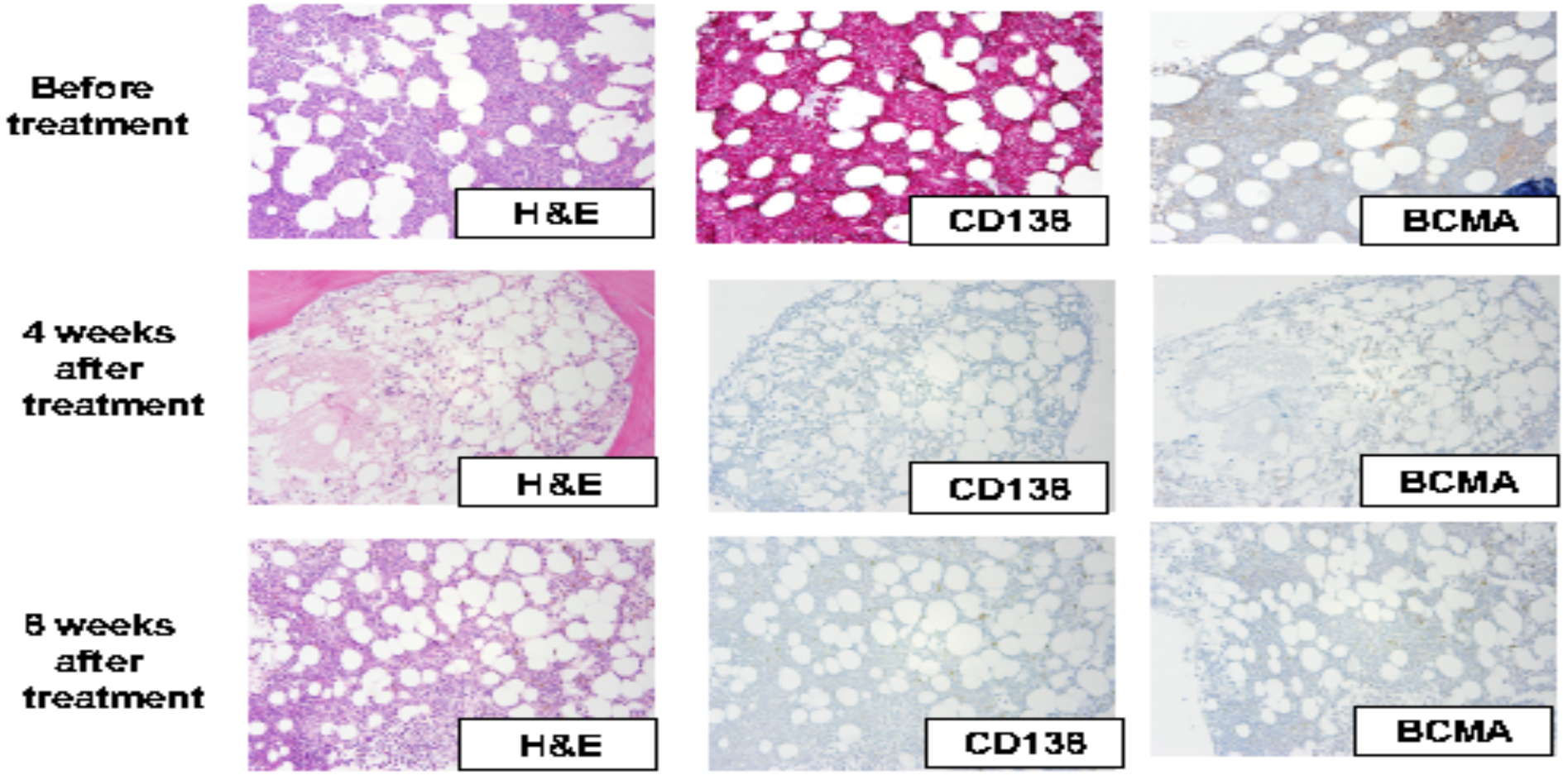
Patient characteristics

Baseline characteristics of patients

- 24 patients treated on study; 2 patients received 2 cell infusions
- Median of 9.5 prior lines of therapy
- 6/15 evaluable patients (40%) with high risk cytogenetics, 5/15 (33%) with deletion 17p
-
- 10/16 patients (63%) refractory to last treatment regimen
- Patients treated on lower dose levels had very similar baseline characteristics as patients treated on highest dose level.

Multiple myeloma reduction

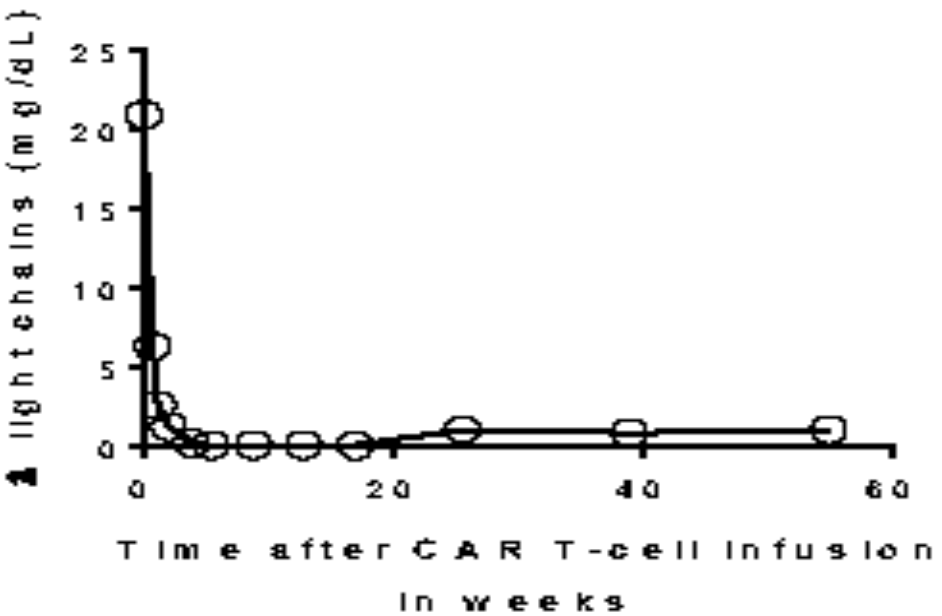
Multiple myeloma that made up more than 90% of Patient 10's bone marrow cells was eliminated after CAR T-cell infusion



Patient 14

Patient 14 attained VGPR of heavily pretreated extramedullary light chain myeloma

- 65 year old male with extramedullary λ light chain multiple myeloma
- Received 16 prior lines of therapy, including 2 autologous stem cell transplants
- He had a rapid decrease of λ light chains after CAR T-cell infusion
- His response was a VGPR that lasted 84 weeks.



Brudno et al. *Journal of Clinical Oncology* 2018

Response summary

Summary of responses of anti-BCMA CAR T at all dose levels

CAR T-cell dose/kg	Response (duration in weeks, + means ongoing)
$0.3x10^6$	PR (2), SD (6), SD (6)
$1x10^6$	SD (12), SD (4), SD (2)
$3x10^6$	SD (7), VGPR (8), SD (16), SD (2)
$9x10^6$	Stringent CR (17), VGPR (66), VGPR (29), VGPR (84), SD (2), VGPR (11), Stringent CR (69), VGPR (34), PR (31), VGPR (82), PD, VGPR (11), sCR (88), PR (2*), PR (29), SD (1)

Patients received no anti-myeloma therapy after infusion of CAR T cells until progression occurred

*Lost to follow-up

Brudno et al. *Journal of Clinical Oncology* 2018

Anti-BCMA CAR T cells

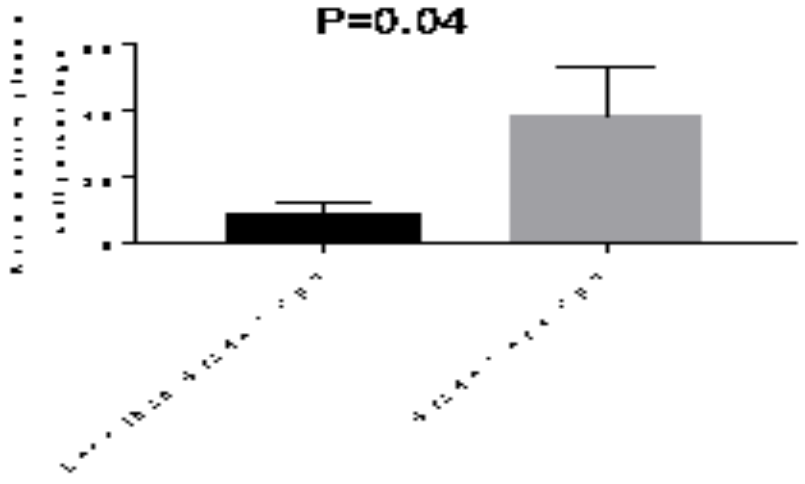
Toxicity of anti-BCMA CAR T cells: cytokines and myeloma burden

Cytokine release syndrome (CRS) on highest dose level (n=16):

- 2 patients with Grade 4
- 4 patients with Grade 3
- 10 patients with <Grade 3 CRS

Immunosuppression for CRS management:

- 5 patients (31%) received tocilizumab for CRS management
- 4 of the patients who received tocilizumab also received corticosteroids for CRS management or adrenal insufficiency



Anti-BCMA CAR T-cell summary

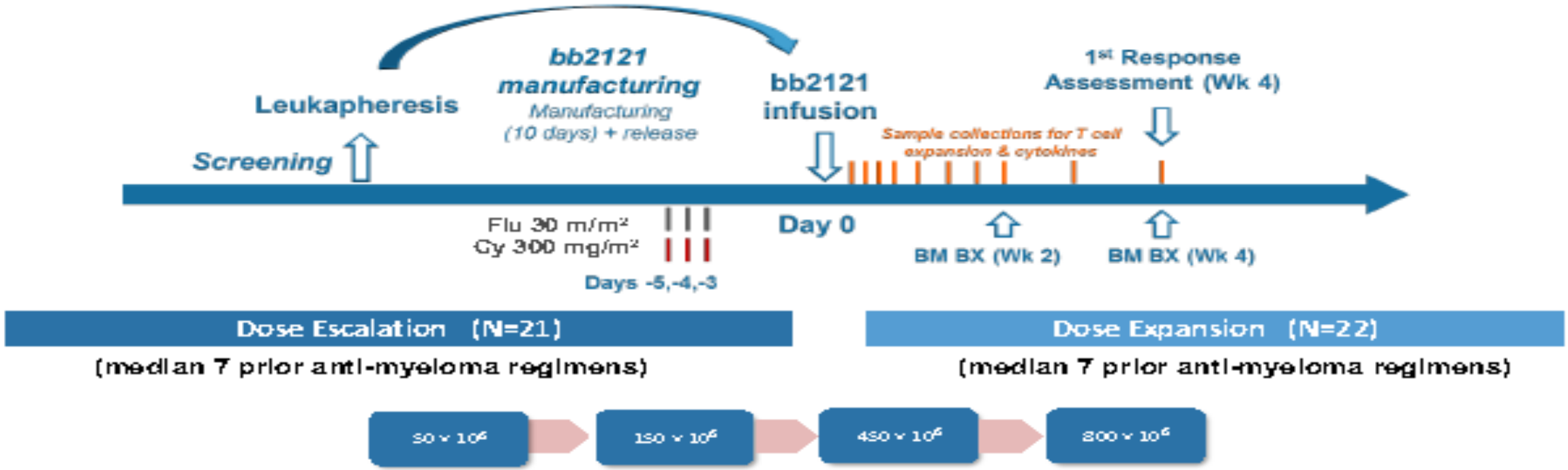
Summary of anti-BCMA CAR T cells at NCI single-center study

- Only 2/10 objective responses on dose levels 1-3
- 13/16 objective responses at optimal dose of $9x10^6$/kg (81% ORR)
- 5 of 16 patients on the optimum dose level have had durations of response of >1 year; 9/16 patients on the optimal dose had responses of >6 months
- Responses allowed patients to be off-therapy for many months
- Multiple myeloma is difficult to treat because of its phenotypic heterogeneity

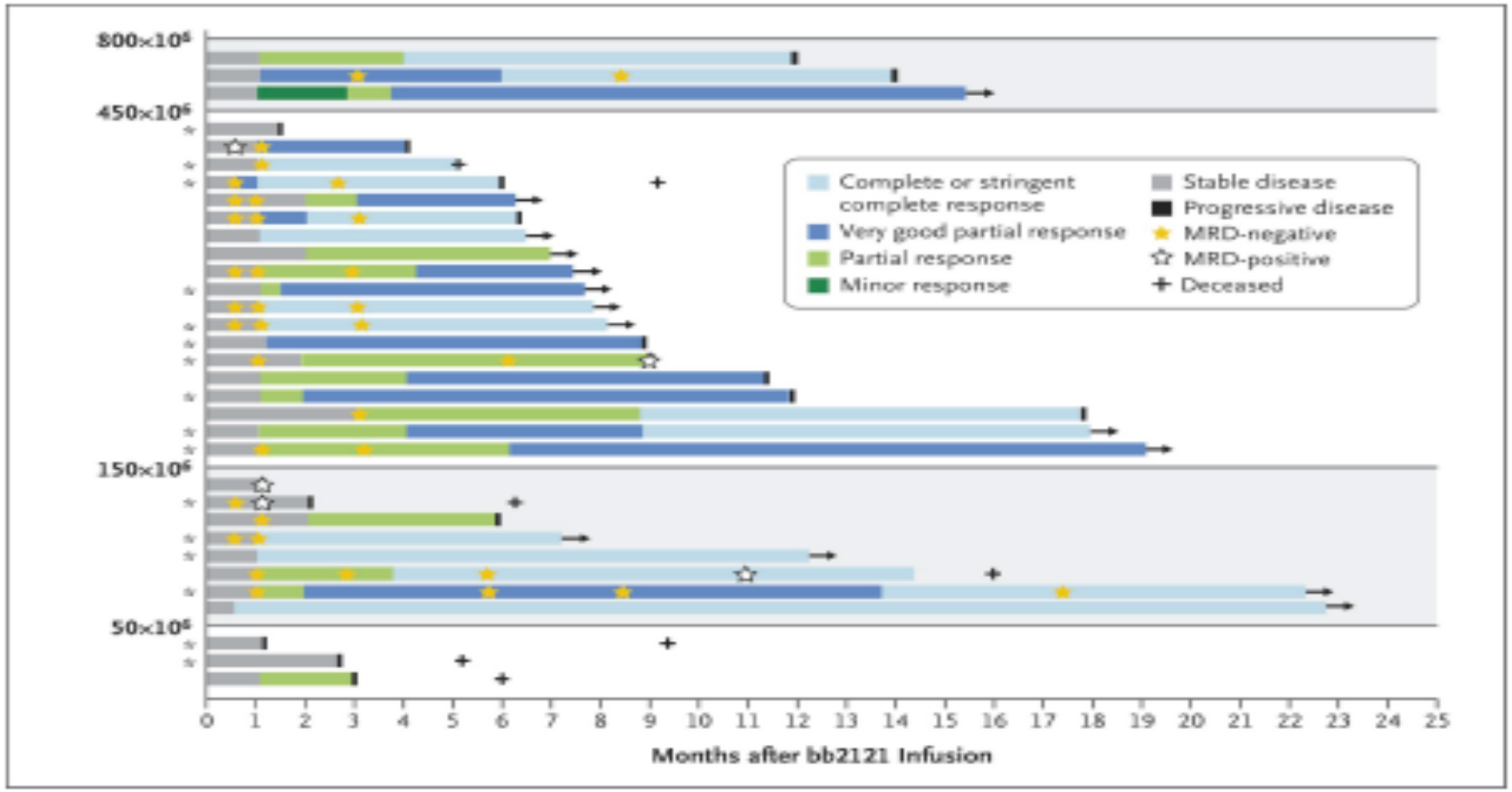
Study CRB401

bb2121 Anti-BCMA CAR T-cell therapy in patients with relapsed/refractory multiple myeloma: updated results from a multicenter phase I study CRB401

- The CAR used in bb2121 had the same 11D5-3 scFv as the previously mentioned CAR used at the NCI.
- The bb2121 CAR had a 4-1BB costimulatory domain and was encoded by a lentivirus



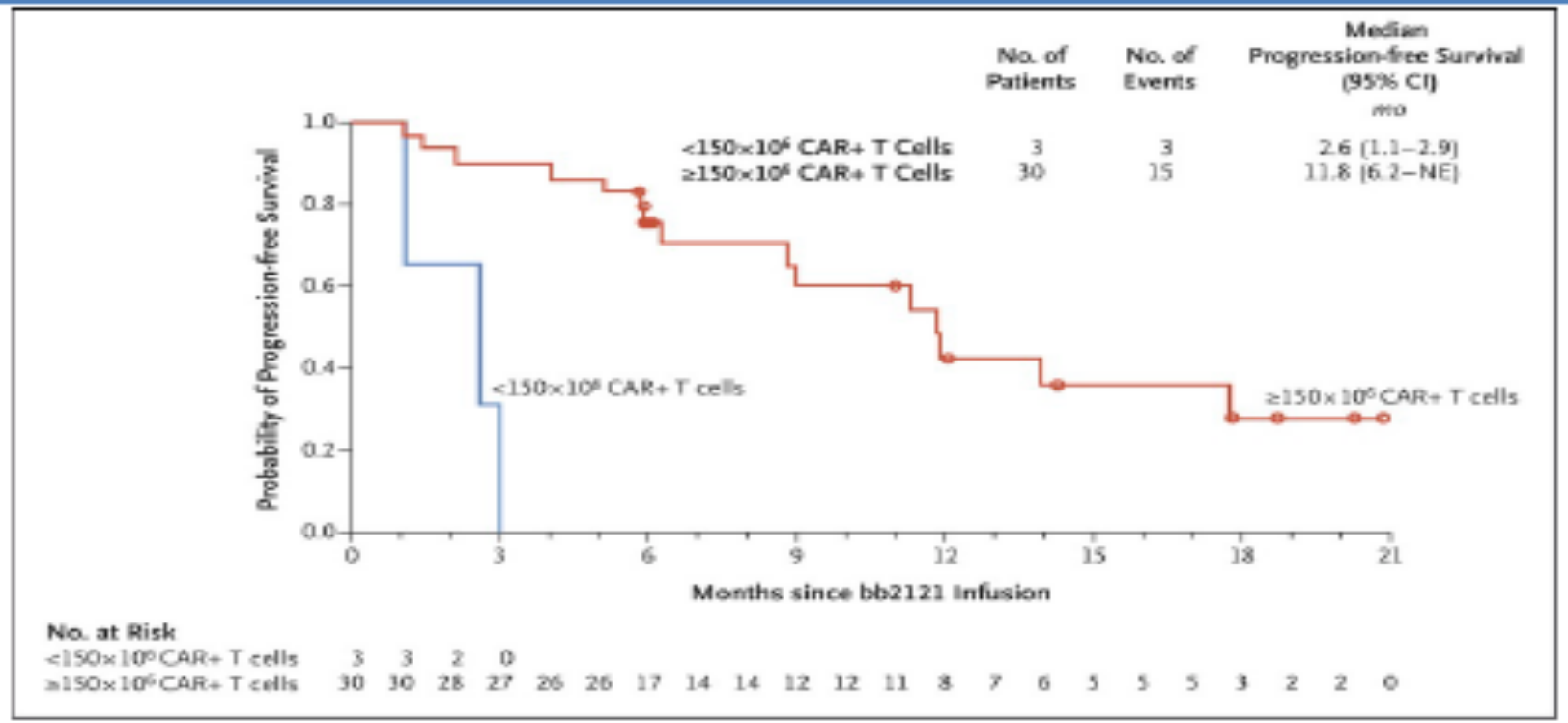
Bb2121 responses



Raje et al. *The New England Journal of Medicine*, 2019

Progression-free survival

Bb2121 progression-free survival



- Cytokine-release syndrome was relatively mild; 2 of 33 patients had Grade 3, and none had Grade 4 CRS
- Only 1 of 33 patients had Grade 3 or 4 neurologic toxicity
- 7 patients received tocilizumab and 4 received corticosteroids

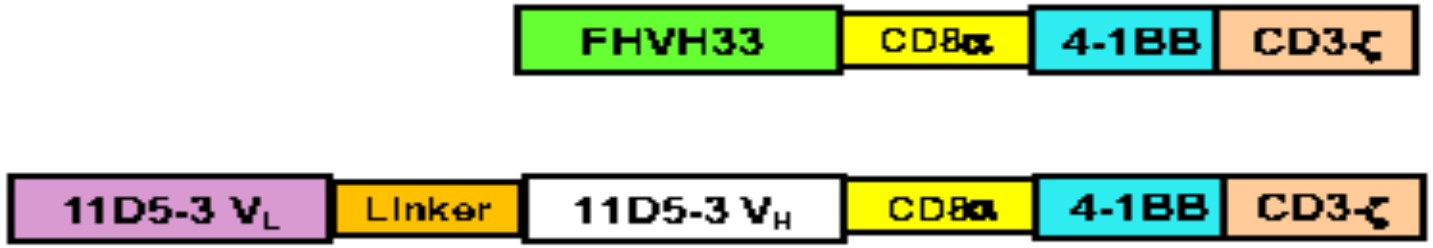
Raje et al. *The New England Journal of Medicine*, 2019

Room for improvement

Room for Improvement:
Development of Fully-Human, Heavy-Chain Only anti-BCMA CAR T-cell Therapy

CARs with heavy chain only

Potential advantages of CARs with heavy-chain-only binding domains led us to develop fully-human heavy-chain-only CARs targeting BCMA



- FHVH: Fully-human heavy chain variable domain generated in a transgenic rat by TeneoBio, Inc.
- Because the heavy-chain-only domains do not have linkers, immune responses directed at linkers and junctions between the linker and variable domains are eliminated.
- Heavy-chain-only binding domains are smaller (good for bispecific CARs).
- In vitro, FHVH33-CD8BBZ function was equivalent to function of a CAR with the 11D5-3 murine scFv used in several clinical trials.

Clinical trail

Clinical trial of FHVH33-CD8BBZ T cells

Eligibility

- Enrolling relapsed multiple myeloma
- Patients need normal cardiac ejection fraction, no history of cardiac problems
- Creatinine maximum 1.5 mg/dL
- Platelets minimum 55/μL
- Must have measurable multiple myeloma and at least 3 lines of prior therapy

Trial design

- Dose escalation
- Conditioning regimen of 300 mg/m² cyclophosphamide and 30 mg/m² fludarabine daily for 3 days
- One infusion of anti-BCMA CAR T cells 3 days after the chemotherapy ends

Demographics

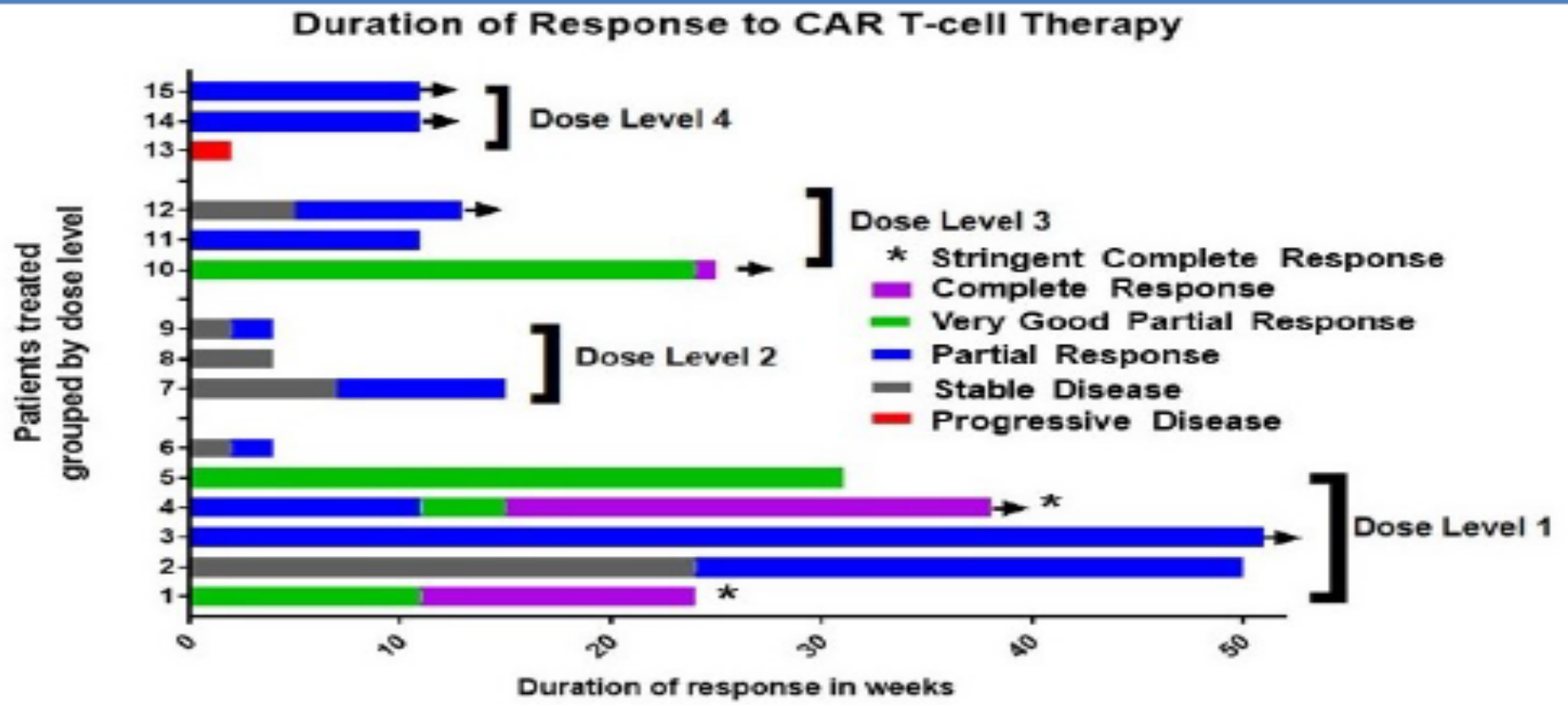
FH-BCMA Demographics

Demographics of Treated Patients

	N or median	%
Total	15	
Age, *median (range)*	64 (41-71)	
Female	9	60%
High risk feature- t(4;14)	6	40%
High risk feature- t(14;16)	1	7%
High risk feature –del17p or TP53	5	33%
≥2 high risk features	4	27%
Prior lines of therapy	6	
Extramedullary disease at baseline	7	47%

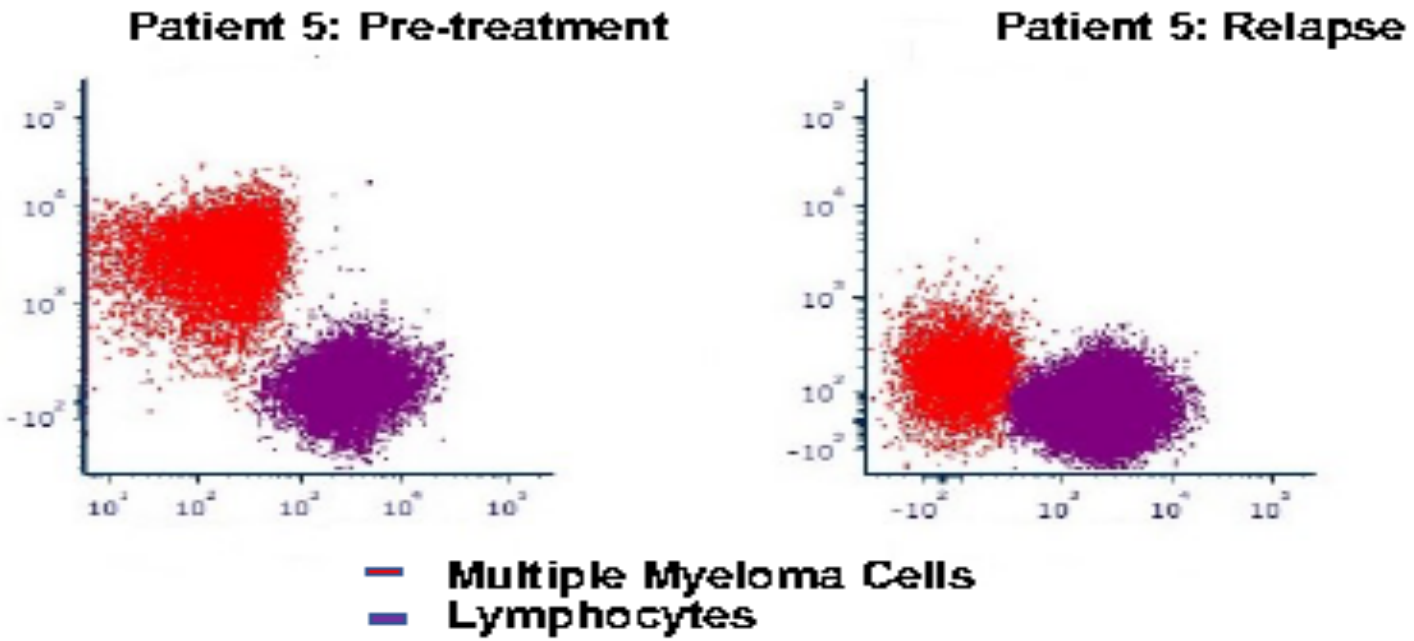
Summary

Summary of responses of anti-BCMA CAR T at all dose levels



Relapse

Relapse with BCMA-negative plasma cells



Out of the 7 patients who have relapsed, 2 patients had evidence of BCMA negative myeloma in the bone marrow and 1 patient had BCMA negative myeloma detected in a new soft-tissue plasmacytoma.

Future plans

Summary and future plans for CAR T-cell therapies of multiple myeloma

- Anti-BCMA CAR T cells have powerful activity against multiple myeloma.
- Anti-BCMA CAR T cells are in international phase II clinical trials, but multiple myeloma is phenotypically heterogeneous, so targeting more than 1 antigen is important.
- More multiple myeloma antigens are needed in addition to BCMA
- Currently at the NCI, we have an actively-recruiting trial of an anti-BCMA CAR with a heavy-chain-only antigen recognition domain.

Acknowledgements

Acknowledgements

James Kochenderfer
Steven Rosenberg

Kochenderfer lab and team
Jennifer Brudno
Katy Cappell
Micaela Ganaden
Brenna Hansen
Rachael Mohn
Ashley Carpenter
Jennifer Mann
Norris Lam
Shicheng Yang
Christina Amatya
Danielle Vanasse

Pathology
Stefania Pittaluga
Maryalice Stetler-Stevenson
Constance Yuan
Alina Dulau

Surgery Branch
Stephanie Goff
Richard Sherry
Jim Yang
Rashmika Patel

Radiology
Mohammadhadi Bagheri

Dept. Transfusion Medicine
David Stroncek
Vicki Fellowes
Jo Procter

Patients and their families